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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,657	DRUMM ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9,16,94,95 and 97-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,9,16,94,95 and 97-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/6/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's amendment to the claims filed 11/12/2009 is acknowledged. With entry of the amendment, claims 1, 4-6, 9, 16, 94, 95, and 97-99 are pending and examined herein.

Applicant's response filed 11/12/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 8/12/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Domestic and Foreign Priority

The previous Action explained that written description support is not found in either of the domestic or foreign priority documents for the claimed invention. In particular written description and/or enabling support is not found in Provisional Application 60/431173 or Foreign Priority Application EP02008761.5 for a method of treating disorders related to angiogenesis, neovascularization, the neurosensory retina, or choroid, or any combination thereof, or for methods of treating wet age-related macular degeneration (AMD), diabetic retinopathy, autosomal recessive retinitis pigmentosa, or congenital stationary night blindness by administration of dsRNAs. Further, no support is found in either of the prior filed applications for methods of treatment further comprising diagnosing a subject with a disorder or predisposition to a disorder of the eye, or isolating the target gene.

To be entitled to the benefits of 35 U.S.C. 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the

invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Thus, with entry of the amendment filed 11/12/2009, the disclosure of the prior-filed applications, Application No. 60/431,173 and EP 02008761.5 fail to provide adequate written description support in the manner provided by the first paragraph of 35 U.S.C. 112 for at least claims 4-6, 9, 95, 97, and 99.

Thus, for purposes of this examination, the earliest effective filing date of claims 4-6, 95, 97, and 99 is considered to be that of PCT/EP03/04003, filed 4/16/03.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)—withdrawn

The rejection of Claims 1, 4-6, 9, 16, and 94-98 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)—maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 99 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

The instant application as filed is not considered to reasonably enable one of skill at the time of filing to use the methods now claimed for treating autosomal recessive retinitis

pigmentosa or congenital stationary night blindness by RNA interference of a target gene without resorting to substantial *de novo* trial and error experimentation and with no assurance of every reaching a successful conclusion, since there is no evidence remotely connecting the treatment of autosomal recessive retinitis pigmentosa or congenital stationary night blindness by inhibiting the expression of any gene and no direction or guidance as to how to achieve the claimed effects other than a general invitation to try. To be sure, the instant application provides no description of any interfering RNAs that should be used in the claimed treatment methods, nor any specific guidance as to how to obtain or identify such therapeutically effective interfering RNAs. In particular the instant application does not identify or name a credible target gene or target site in any target gene, wild type or mutant, that should be used for the design of the interfering RNAs required by the methods of claim 99.

A reasonable correlation between the inhibition of any target gene and the treatment of autosomal recessive retinitis pigmentosa or congenital stationary night blindness has not been identified or reasonably established by the instant application, and is not readily apparent from the prior art. Thus, the scope of the claims is not commensurate with enabling support provided by the application as filed.

The claims are drawn to methods of treating autosomal recessive retinitis pigmentosa or congenital stationary night blindness in the eye of a subject, comprising administering to a subject a short interfering double stranded RNA corresponding to mRNA of a target gene. The specification teaches and the extrinsic literature confirms that SEQ ID NO:3, a 3231-nucleotide DNA, corresponds to human phosphodiesterase 6B, cGMP-specific, rod, beta (PDE6B) mRNA (accession No. NM_000283). The specification teaches and the extrinsic evidence confirms that

malfunction of this gene, and more specifically, missense or nonsense mutations in this gene are associated with autosomal recessive retinitis pigmentosa, or congenital stationary night blindness 3 (CSNB3). See, for example, Dryja et al. (1995) "Mutations in the gene encoding the alpha subunit of the rod cGMP-gated channel in autosomal recessive retinitis pigmentosa" *PNAS* 92:10177-10181. Weber et al. (1991) "Genomic organization and complete sequence of the human gene encoding the 3-subunit of the cGMP phosphodiesterase and its localisation to 4p16.3" *Nucleic Acids Res.* 19:6263-6268 (of record), also taught that the conditions associated with autosomal recessive retinitis pigmentosa (RP) stem from an insufficiency of cGMP phosphodiesterase not an overabundance, stating at page 6267 that:

> Recently, evidence has been provided that the degenerative process in the retinal degeneration (rd) mouse is caused by a defect in the β-subunit of the rod cGMP PDE (8). The rd mouse is considered an animal model for autosomal recessive retinitis pigmentosa (RP) as homozygous mice have been shown to display hereditary progressive degeneration of retinal photoreceptors (36, 37). Retinal degeneration in these mice is preceded by elevated levels of cGMP in the retina as a result of deficient cGMP PDE activity (38, 39).

Hart et al. (2005) "Genotype–Phenotype Correlation of Mouse *Pde6b* Mutations" *Investigative Ophthalmology and Visual Science*. 2005;46:3443-3450 (post filing art) teaches that defects in photoreceptor phosphodiesterase activity caused by mutations in the ß subunit of the rod cGMP-phosphodiesterase (*PDE6B*) gene have been shown to underlie cases of arRP accounting for ~1% to 2% of all cases of RP. It is further taught the product of *Pde6b* contributes to the heterotetrameric phosphodiesterase complex (PDE, $\alpha\beta\gamma_2$), which regulates cytoplasmic cGMP levels in rod photoreceptors in response to light. On light stimulation, PDE is activated by removal of the γ-inhibitory subunits, resulting in a decrease in cGMP levels and hyperpolarization of the rod cell. In mice with the retinal degeneration 1 (*rd1*) mutation elevated

cGMP levels persist because of a homozygous null mutation in the *Pde6b* gene. This results in permanent opening of cGMP-gated cation channels in the membrane of the rod photoreceptors, allowing an excess of extracellular ions to enter the cell, which ultimately leads to cell death by apoptosis.

Altogether, then, the evidence suggests that further suppressing the expression of PDE, as in the method now claimed, would only further exacerbate the night blindness or retinitis pigmentosa present in the subject. While the application as filed disclosed the putative association between mutant PDE and the conditions recited in claim 99, the application provides no credible or specific solution for treating the disease by RNA interference. The application describes no exemplary small interfering RNAs, names no particular target sites, and suggests no viable target gene for treating the conditions named. It is unclear then how one of skill could practice the claimed method to treat congenital autosomal recessive retinitis pigmentosa or congenital stationary night blindness without resorting to *de novo* trial and error research.

In fact studies published prior to and after the filing date of the instant application show that suppressing the expression of rod cGMP phosphodiesterase subunits in animals using either ribozymes or antisense oligonucleotides actually lead to photoreceptor and bipolar cell degeneration, conditions associated with retinitis pigmentosa. Indeed researchers have used antisense and ribozyme-mediated degradation of the genes encoding either the gamma or alpha subunits of rod cGMP-gated channel protein, a cGMP phosphodiesterase, to produce animal models of human retinitis pigmentosa. See, for example, Liu et al. (2005) "Ribozyme Knockdown of the [gamma]-Subunit of Rod cGMP Phosphodiesterase Alters the ERG and Retinal Morphology in Wild-Type Mice" *Investigative Opthalmology & Visual Science* 46:3836-

3844; and Leconte et al. (2000) "Impairment of rod cGMP-gated channel alpha-subunit expression leads to photoreceptor and bipolar cell degeneration" *Invest Ophthalmol Vis Sci*. 2000 Mar;41(3):917-26.

While the prior and post filing art clearly correlates autosomal recessive retinitis pigmentosa with a deficiency of functional cGMP-gated channels or cGMP phosphodiesterase (PDE) likely caused by certain nonsense and missense mutations in the gene, neither the specification nor the prior or post-filing art teaches or suggests any link between inhibiting the expression of PDE6B or its mutant alleles and the treatment of the diseases named in claim 99. There is no evidence in the prior art or the specification of any correlation between reducing the expression of any target gene or variant allele and treatment of retinitis pigmentosa or night blindness. Indeed, the literature teaches that it is not the overexpression of phosphodiesterase or its protein product that leads to RP or any other eye disease but the lack of functional phosphodiesterase protein (i.e., paucity of protein) that may be the cause of RP or night blindness. See, for example, Dryja et al., cited above. Even the name, "autosomal recessive," suggests that RP night blindness disorder associated with phosphodiesterase protein is not the result of the expression of an abnormal dominant protein but the lack of normal protein essential to eye function. Thus, it is unclear, and the specification does not show or explain how the further repression of phosphodiesterase or, for that matter, any other gene target would improve the vision or visual acuity of any subject, particularly those having autosomal recessive retinitis pigmentosa or congenital stationary night blindness. On the contrary it would appear prima facie the expression of the wild type gene should be enhanced or restored to treat the disease, which is not a method within the scope of what is now claimed.

Furthermore, a review of the specification and the prior art fails to find a single working example showing or adequately representing that inhibiting the expression of an mRNA encoding wild-type or mutant PDE6B (such as instant SEQ ID NO:3) or any other target gene produces an effect correlative of treatment in any animal suffering from autosomal recessive retinitis pigmentosa or congenital stationary night blindness. Neither the prior art nor the specification establishes any nexus between the inhibition of a target gene and the treatment of each of these diseases. Accordingly, it is reasonable to question the objective truth of the assertions in the claims that the administration of an interfering dsRNA targeting PDE (e.g., SEQ ID NO:3) or any other target gene may be used to treat each of the disorders recited therein. With no examples to draw on and no direction or guidance of any kind in the specification showing how or even whether inhibition of a target gene or any isoform thereof may be used to treat each of these disorders named in claim 99 one of skill would necessarily need to resort to *de novo*, trial and error experimentation to achieve the claimed effects, and with no assurance of ever reaching a successful conclusion. The effects promised by the claims represent hoped-for functions---a starting point for further research, but nothing more. Such research, in the absence of any direction, guidance, or assurance by the specification, is considered to be undue.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

Applicant's arguments filed 11/12/2009 traversing the enablement rejection have been considered but are not persuasive.

MPEP 2164.04 states In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

The Examiner respectfully refers to the rejection and submits he has met his burden in this regard.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4-6, 94, 95, 97, and 98 are rejected under 35 U.S.C. 102(e) as being anticipated by King (US 20020165158 A1).

King et al. taught methods for treating angiogenesis-related disorders, including diabetic retinopathy and other neovascular disorders of the eye comprising administering a short interfering double stranded RNA (siRNA) specific for PKCβ mRNA (page 1, 6, 8, 10, and 11, and see claims for example). PKCβ2 is said to enhance VEGF-induced cell proliferation in, for example, retinal cells, which in turn leads to increased angiogenesis. (paragraph 4).

It is taught the siRNA may be administered orally, systemically, transmucosally, or as aqueous eye drops, cream, lotion or other vehicle suitable for administration onto the eye surface (paragraph 125 and 184, page 10, and paragraph 190), all modes of delivery outside the blood brain barrier. Preferably the agent that modulates PKCβ (e..g, siRNA, paragraph 6) is targeted to the retinal tissue (paragraph 184 and see entire disclosure, including claims). Additionally, it is said that the pharmaceutical composition may be administered directly into a retinal tissue, arthritic tissue, or tumor tissue of the subject (paragraph 194). Several types and forms of

compositions for delivery to the eye are described (page 10). The administration is designed to inhibit the expression and activity of PKCβ in retinal tissue (see claims and disclosure).

With regard to claim 95, King taught that in a preferred embodiment, the subject has or is at risk for an angiogenesis-related disorder, e.g., retinopathy, e.g., oxygen-induced retinopathy-of-prematurity, oxygen-induced retinopathy, or diabetic retinopathy (paragraph 10). Therefore, the diagnosis is implied. With regard to claim 97, it is implied with any treatment method designed specifically to inhibit the expression of a gene, the researcher or clinician would necessarily monitor the inhibition by suitable assays of patient samples for target mRNA levels.

Accordingly, King et al. anticipate the instant claims.

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Claims 4-6, 95, and 97 are rejected under 35 U.S.C. 102(e) as being anticipated by Tolentino et al. (U.S. Patent 7,148,342).

Tolentino et al. had disclosed methods for treating diabetic retinopathy, age-related macular degeneration (a condition characterized by choroidal neovascularization), and other angiogenesis-related disorders of the eye comprising administering a small interfering RNA to the subject. At column 15 it is said the siRNA of the invention can be administered to the subject by any means suitable for delivering the siRNA to the cells of the tissue at or near the area of neovascularization. For example, the siRNA can be administered by gene gun, electroporation, or by other suitable parenteral or enteral administration routes. Suitable enteral administration routes are said to include oral, rectal, or intranasal delivery. Suitable parenteral administration routes include intravascular administration (e.g. intravenous bolus injection, intravenous infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the

vasculature); peri- and intra-tissue injection (e.g., peri-tumoral and intra-tumoral injection, intra-retinal injection, or subretinal injection); subcutaneous injection or deposition including subcutaneous infusion (such as by osmotic pumps); direct application to the area at or near the site of neovascularization, for example by a catheter or other placement device (e.g., a retinal pellet or a suppository or an implant comprising a porous, non-porous, or gelatinous material); and inhalation. It is preferred that injections or infusions of the siRNA be given at or near the site of neovascularization. With regard to claim 97, at columns 11 and 12 it is said RNAi-mediated degradation of the target mRNA can be detected by measuring levels of the target mRNA or protein in the cells of a subject, using standard techniques for isolating and quantifying mRNA or protein as described above.

Accordingly, Tolentino et al. anticipated the instant methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-6, 9, 16, 94, 95, 97, and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (US Patent 5,814,620) in view of:

1. Tuschl et al. (US Patent Application 2004/0259247 A1); and
2. Bass (2001) *Nature* 411:428-9; and
3. Pardridge (US 2002/0054902 A1).

Robinson et al. taught methods for delivering antisense oligonucleotides intraocular to cells in the eye to treat diseases associated with the eye, including diabetic retinopathy and macular degeneration (pp. 1-18). The antisense oligonucleotide may be composed of ribonucleotides, deoxyribonucleotides, or a combination thereof (column 7, lines 30-35; claim 5), and combined with a variety of pharmaceutically acceptable carriers for intraocular, intravitreal, or systemic administration (column 10, lines 20-40; column 11, lines 5-15). For example, Robinson et al. taught that "Intravitreal injections of oligonucleotides against VEGF can be an effective means of inhibiting retinal neovascularization in an acute situation. However for long term therapy over a period of years, systemic delivery (intraperitoneal, intramuscular, subcutaneous, intravenous) either with carriers such as saline, slow release polymers, or liposomes should be considered" (column 11). Similarly at columns 9 and 10, Robinson et al.

taught that the synthetic oligonucleotide could be administered by intraocular, oral ingestion, inhalation, or cutaneous, subcutaneous, intramuscular, or intravenous injection.

Thus, Robinson taught and suggested using therapeutic oligonucleotides such as antisense oligonucleotides to treat eye disease, and specifically recommended and showed that said therapeutic oligonucleotides may be delivered by virtually any known route including systemic administration and intraocular injection.

While Robinson et al. taught methods and materials making and using antisense oligonucleotides to treat eye diseases, Robinson et al. do not teach siRNAs.

Tuschl et al. taught the methods and materials for making and using short double-stranded interfering RNA molecules (siRNAs) for inhibiting the expression of virtually any known mammalian gene in cells in vitro and in vivo for research and therapeutic purposes (pp. 1-16). It is taught that double-stranded RNA molecules 19-25 nucleotides in length have RNAi activity and may trigger the specific degradation of homologous RNAs within the region of identity with the dsRNA (paragraphs 5, 7, 11, and 17 for example). Tuschl et al. teach that siRNA duplexes are preferably composed of 21-nt antisense siRNAs and should be selected to form a 19-bp double helix with 2-nt 3' overhanging ends (paragraphs 9, 11, 179). In summary, the Tuschl et al. reference is considered to be a complete blueprint for the design, synthesis, and use of short interfering, double-stranded RNA, in modified or unmodified forms, against any desired target gene. The reference contains detailed descriptions and several examples typifying the use of siRNA in cell culture, and the Application Publication expressly suggests the use of siRNA *in vivo* for use in therapeutic and clinical settings (paragraphs 31-36).

Importantly, Tuschl et al. also compare siRNA methodology to that of antisense and ribozyme techniques for inhibiting gene expression. At paragraph 148, for example, Tuschl et al. state that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments. At paragraph 137, Tusch et al. state that the remarkable finding that synthetic 21 and 22 nt siRNA duplexes can be used for efficient mRNA degradation provides new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNAs may be effective in mammalian systems where long dsRNAs cannot be used due to the activation of the PKR response. As such, the siRNA duplexes represent a new alternative to antisense or ribozyme therapeutics.

Bass teaches that, like some antisense oligonucleotides, which trigger RNase H-catalyzed cleavage of their targets, siRNAs trigger the degradation of complementary messenger RNAs (page 428 and Fig. 1). A general outline of the RNAi mechanism is taught, showing how siRNA-mediated RNAi may be used to interfere with gene expression using siRNAs directed against specific mRNA sequences (Fig. 1). Bass teaches that RNAi has repeatedly proven itself to be more robust that antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. Furthermore, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments.

Pardridge taught immunoliposomes for delivering therapeutic genes across the blood brain barrier into cells in the eye for the treatment of ocular diseases, and showed that it is

possible to obtain expression of an exogenous gene throughout the retina following intravenous injection of a non-viral preparation (cols. 1-18).

Thus, the prior art teaches, in general, that siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligos can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell. For example, Bass teaches that antisense RNA is another technique to prevent the expression of particular genes (page 429). Thus, in this sense, siRNAs and antisense oligos are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.)

Nevertheless, as explained above, siRNAs possess certain advantages over antisense oligos, which would motivate one of ordinary skill in the art to select siRNAs over antisense oligos to more efficiently block and/or reduce the expression of any given target gene, particularly a gene known to be involved in cancer.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to make and use siRNAs, as taught by Tuschl et al. and Bass, for any of the methods disclosed by Robinson et al. for treating eye disease. Further, it would have been obvious to administer said siRNAs by any of the means disclosed by Robinson et al, including systemic. It would also have been obvious to apply the siRNAs directly to the area affected by the disease—the eye—by direct application, injection, or topically, as by eye drops. There is nothing in the art nor any evidence of record showing any express teaching away from the use of

eye drops for the administration of any oligonucleotide-based therapeutic. It is a matter of common sense to apply the therapeutic agent directly to the area of treatment.

Given that Tuschl et al. and Bass teach that siRNAs are in general more potent than antisense oligonucleotides for reducing gene expression in cells, one of skill would have been motivated to substitute siRNAs for antisense oligonucleotides in the methods of Robinson et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571)272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
February 8, 2010